CONFIDENTIAL

Study code: 3000-4210
(Old code 3000-IIIF2-010)

Study title:

Hydroxymatairesinol. Effect on cardiovascular and respiratory function in the telemetred dog.

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RCC Study Number 780625

Hydroxymatairesinol:

Effect on cardiovascular and respiratory function in the telemetered dog

Final Report

Authors: Dr. K.M. Bray-French, M. Gisin

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RCC

TABLE OF CONTENTS

1 PREFACE

1.1 GENERAL

Title	Hydroxymatairesinol: Effect on cardiovascular and respiratory function in the telemetered dog
Sponsor	Hormos Nutraceutical Ltd. Tykistökatu 6A, Biocity Turku, FIN-20520 Finland
Study Monitor	Dr. Helena Korte
Test Facility	RCC Ltd Toxicology Division 4452 Itingen / Switzerland

1.2 RESPONSIBILITIES

Study Director	Dr. K.M. Bray-French
Deputy Study Director	Dr. J.R. Dubach-Powell
Technical Coordinator	M. Gisin
Laboratory Coordinators	D. Hussherr / R. Jenni
Veterinarian	Dr. K. Weber
Head of RCC Quality Assurance	I. Wüthrich

1.3 SCHEDULE

Acclimatisation start	08 August, 2000
Start of surgery	18 August, 2000
Experimental Starting Date	02 October, 2000
Experimental Completion Date	18 October, 2000
Final Report	25 October, 2001

1.4 ARCHIVING

RCC Ltd (4452 Itingen / Switzerland) will retain the study plan, raw data, a sample of test item and the final report of the present study for at least ten years. No data will be discarded without the Sponsor's consent.

1.5 SIGNATURES

STUDY DIRECTOR: Dr. K.M. Bray-French

KM Bray-French

date: 25-OCT-2001

DEPUTY FOR STUDY DIRECTOR: Dr. J.R. Dubach-Powell

JRDubach

date: 25-OCT-2001

TECHNICAL CO-ORDINATOR: M. Gisin

M. G.

date: 25-OCT-2001

MANAGEMENT: S. J. Corney

S. Corney

date: 25-Oct 2001

1.6 QUALITY ASSURANCE STATEMENT

RCC LTD, TOXICOLOGY DIVISION, 4452 ITINGEN / SWITZERLAND

STATEMENT

RCC STUDY NUMBER:	780625
TEST ITEM:	Hydroxymatairesinol
STUDY DIRECTOR:	Dr. K.M. Bray-French
TITLE:	Hydroxymatairesinol: Effect on cardiovascular and respiratory function in the telemetered dog

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The study plan and this report were audited by the RCC Quality Assurance Unit. The dates are given below:

Dates and types of QAU inspections/audits		Dates of reports to the study director and to management
14-AUG-2000	Study plan audit	14-AUG-2000
18-AUG-2000	Study based inspection (surgery and raw data)	18-AUG-2000
02-OCT-2000	Study based inspection (Test item, dose preparation, treatment)	02-OCT-2000
13-15-DEC-2000	Report audit	15-DEC-2000
02-OCT-2001	Report audit	02-OCT-2001

This statement also confirms that this final report reflects the raw data.

Quality Assurance Unit

(for) P. Stolz

Thomas Frei

date: 25 October 2001

GOOD LABORATORY PRACTICE

1.7 STATEMENT OF COMPLIANCE

RCC STUDY NUMBER:	780625
TEST ITEM:	Hydroxymatairesinol
STUDY DIRECTOR:	Dr. K.M. Bray-French
TITLE:	Hydroxymatairesinol: Effect on cardiovascular and respiratory function in the telemetered dog

This study was performed in compliance with:

Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C (97)186/Final].

These procedures are consistent with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHW, MAFF and MITI).

There were no circumstances that may have affected the quality or integrity of the data.

Study Director: Dr. K.M. Bray-French

KMBray-French

date: 25-OCT-2001

1.8 REFERENCES

Validation of a telemetry system for measurement of blood pressure, electrocardiogram and locomotor activity in beagle dogs. Gelzer, A. R. & Ball, H. A. (1997). Clin. Exp. Hypertens. 19, 1135 – 60.

Validation of the ART telemetry system for measurement of blood pressure, electrocardiogram, body temperature and locomotor activity in the dog. Bray-French, K. M. & Hussherr, D. (2000). RCC Project 903587.

2 PURPOSE

The purpose of this study was to evaluate possible pharmacological effects of the test item on the cardiovascular and respiratory systems of the conscious (telemetry) dog when given orally.

3 MATERIALS AND METHODS

3.1 TEST SYSTEM

Test system	Pure-bred beagle dogs, dewormed and vaccinated against distemper, leptospirosis, contagious hepatitis, parainfluenza, parvovirus and rabies.
Rationale	Commonly used for studies of this type.
Source	RCC Ltd Biotechnology & Animal Breeding Division 4414 Füllinsdorf / Switzerland
Total number of animals	4 males
Age at acclimatisation	11 - 19 months
Body weight range at surgical implantation of transmitter	7.8 – 9.7 kg
Age at first treatment	13 – 21 months
Body weight range at first treatment	7.2 – 9.9 kg
Identification	Individual kennel number, ear tattoo and implant number.
Number allocation	Animals were allocated a number (1 - 4) on allocation to the study prior to the first treatment.
Acclimatisation	10 days before the transmitter implantation and at least 3 weeks after implantation. A veterinary examination was performed on all animals during the acclimatisation phase to assure a satisfactory health status.

3.2 HUSBANDRY

Room number - acclimatisation - testing	 1U 02 1U 10
Conditions	Standard Laboratory Conditions. Room environment was monitored continuously. Air conditioned with approximately 20 air changes per hour, with target ranges for room temperature 20 ± 3°C and relative humidity 30-70%. Pen floor temperature was maintained at 21 ± 4°C. 12 hours fluorescent light/12 hours dark (light period between 6.00 and 18.00), music during the light period.
Accommodation	Individual kennel with at least 2 square meters floor space per dog.
Diet	350 g pelleted standard Kliba 3353 dog maintenance diet (Provimi Kliba AG, 4303 Kaiseraugst, Switzerland) presented at approximately the same time each day. On the day before each treatment the diet was withdrawn at least 16 hours before dosing. On the treatment days, food was presented after the respiratory parameters measurement at approximately 4 hours after dosing. Batch Nos. 22/00 and 23/00: Results of representative analyses for contaminants are retained in the raw data.
Water	Community tap water from Itingen, *ad libitum*. Representative results of analyses for contaminants are retained in the raw data.

3.3 TEST ITEM

(Information as provided by the sponsor)

Identity	Hydroxymatairesinol
Description	Solid, labile
Batch number	T011-B304P1
Purity	>95%
Molecular weight	374.39
Storage	In the refrigerator at 2 – 8°C
Expiry date	31 July, 2001
Safety precautions	Routine hygienic precautions were employed to assure personnel health and safety.

3.4 EQUIPMENT

Recording (telemetry)	Telemetry system (Data Sciences Inc., St. Paul, Minnesota, USA) consisting of: implantable transmitter unit (TL11M2-D70-PCT) for the measurement of blood pressure, electrocardiogram and locomotor activity, cage receiver (RMC-1), ambient pressure monitor (APR-1), a consolidation matrix (DEM) and a PC-based data acquisition system using Dataquest™ Advanced Research Technology (A.R.T.™) software.
Recording (respiratory parameters)	PC with Pulmonary Monitoring System (PMX) software (Mumed Ltd., London, England) connected to a pneumotachograph and a physiological recorder (PR 800).

3.5 IMPLANTATION OF TELEMETRY TRANSMITTERS

3.5.1 INDUCTION OF ANAESTHESIA

Identification of anaesthetic	Thiopental
Source	Provet AG, 4321 Lyssach, Switzerland
Batch number	33056TF
Expiry date	09/2000
Route of administration	Intravenous
Dose	Sufficient volume of a 5 % solution to induce anaesthesia.
Thiopental preparation	Will be used as supplied
Storage	Refrigerated (approx. 4°C) in the dark

3.5.2 MEDICATION

Identification of medication	Atropine sulphate
Source	Amino AG, 5432 Neuenhof, Switzerland
Batch number	4016/1
Expiry date	01/2002
Route of administration	Intramuscular
Concentration of dosing solution	0.1 mg atropine/ml
Dose	Approximately 1 ml
Dosing solution preparation	The stock solution of 1 mg/ml will be diluted to a final concentration of 0.1 mg/ml with saline.
Storage	Refrigerated (approx. 4°C) in the dark

3.5.3 MAINTENANCE OF ANAESTHESIA

Identification of anaesthetic	Halothane
Source	Arovat AG, Zollikon / Switzerland
Batch number	E39818
Expiry date	12/2004
Route of administration	Inhalation
Concentration in air	2-3 %
Concentration level rationale	Sufficiently high to maintain anaesthesia
Halothane preparation	Was used as supplied
Storage	Refrigerated (approx. 4°C) in the dark

3.5.4 SURGICAL IMPLANTATION OF TRANSMITTERS

This procedure was performed at least 3 weeks before the experimental starting date. Animals were fasted overnight (at least 16 hours) before surgery. After induction of anaesthesia with thiopental and medication with atropine sulphate, the animal was prepared for surgery, which was performed under aseptic conditions. Anaesthesia was maintained with halothane. Body temperature was maintained by means of a thermal heating pad.

An incision line (approx. 10 cm) was made in the upper left flank and a subcutaneous pocket formed. The tabs of the implant were sutured to the underlying tissue to maintain its orientation. The pressure catheter was tunneled subcutaneously from the flank to the groin where a branch of the femoral artery (A. caud. femoris media or A. genus descendens) was isolated and catheterised. The catheter tip was advanced into the femoral artery (while monitoring the telemetered pressure signal) for approximately 20 cm and secured with silk ligatures. A sufficient catheter length was provided to allow normal extension of the leg. One of the biopotential leads was placed subcutaneously terminating near the right axilla, the other was secured in the area of the lower left abdomen (Lead II configuration).

All incisions were closed by standard surgical procedures and were sprayed with tetracycline wound spray. After surgery the animal was placed into a warm environment and its recovery monitored.

Post operative antibiotics (Baytril®, 3ml sc) were administered on the day of operation and thereafter once per day for 2 days and the analgesic Buprenorphine (0.01 – 0.02 mg/kg sc) was administered once on the day of operation and thereafter twice per day for 3 days following surgery.

A period of at least 3 weeks was allowed for recovery of animals. Once the animals had recovered an implant viability check was performed. It was noted that the electrocardiogram leads from two animals had come loose or were broken. These dogs were reoperated (subcutaneous surgery) and the following day a second viability check was performed to ensure that clear signals could be obtained. A period of five days was allowed for recovery of the animals before the first dosing.

3.6 SHAM DOSING

Animals were sham dosed with an empty capsule, 2 times during the acclimatisation phase. Animals were also trained to accustom them to the pulmonary monitoring system equipment, four times prior to the first treatment.

Following both sham procedures, no telemetry or respiratory parameters were recorded.

3.7 CAPSULE PREPARATION

Dose levels are in terms of test item as supplied.

The appropriate amount of test item was weighed directly into gelatin capsules. The individual weights of the test item required for administration were adjusted based on body weight.

Empty capsules of the same size and number as those given for the high dose level were administered for the control treatment. Capsules were prepared on each day of treatment.

3.8 TREATMENT

Method /dose route	Oral (capsule). Animals were fasted overnight with access to water *ad libitum.*
Rationale	Clinical route of administration
Treatment	Each of the four animals (1 - 4) received four oral doses with 4-8 days between each treatment.
Dose levels	The following doses were given to each animal using a randomised design:

Date	**02.10.2000**	**06.10.2000**	**10.10.2000**	**18.10.2000**
Animal 1	0 mg/kg Hydroxymatairesinol	20 mg/kg Hydroxymatairesinol	2 mg/kg Hydroxymatairesinol	200 mg/kg Hydroxymatairesinol
Animal 2	0 mg/kg Hydroxymatairesinol	20 mg/kg Hydroxymatairesinol	2 mg/kg Hydroxymatairesinol	200 mg/kg Hydroxymatairesinol
Animal 3	200 mg/kg Hydroxymatairesinol	2 mg/kg Hydroxymatairesinol	20 mg/kg Hydroxymatairesinol	0 mg/kg Hydroxymatairesinol
Animal 4	200 mg/kg Hydroxymatairesinol	2 mg/kg Hydroxymatairesinol	20 mg/kg Hydroxymatairesinol	0 mg/kg Hydroxymatairesinol

	Doses are in terms of test item as supplied. Each animal was weighed on the day of treatment and the dose was adjusted according to body weight.
Rationale for dose level selection	Requested by the Sponsor.
Frequency of administration	Once for each dose level at approximately the same time on each day of administration.

3.9 OBSERVATIONS

The following observations were recorded:

Body weights	On test day prior to dosing or on the day of dosing
Cardiovascular parameters (systolic, diastolic and mean blood pressure & heart rate)	Recorded for at least 60 minutes before dosing and for at least 12 hours after dosing. Mean values over 5 minutes, obtained at -60, -30, 30 minutes, 1 hour and thereafter every hour for 12 hours after dosing were reported.
Electrocardiogram	Recorded for at least 60 minutes before dosing and for at least 12 hours after dosing. Values obtained at -60, -30, 30 minutes, 1, 2, 3, 4 and 12 hours after dosing were reported. P-wave duration and amplitude, P-Q, QRS and Q-T intervals were measured manually from the traces and reported.
[1]Respiratory parameters (respiratory rate, tidal volume & minute volume	Recorded for two 5 minute periods before dosing and for 5 minutes at approximately 1, 2 and 4 hours after dosing. Mean values over 5 minutes were reported.
Clinical signs	Recorded before dosing, shortly after dosing and at approximately 1, 2, 4 and 24 hours after dosing.
Locomotor activity	Recorded for at least 60 minutes before dosing and for at least 12 hours after dosing. Mean values over 5 minutes, obtained at -60, -30, 30 minutes, 1 hour and thereafter every hour for 12 hours after dosing were reported.

Systolic, diastolic and mean blood pressures and heart rate were obtained from the femoral artery waveform. Locomotor activity was calculated by measurement of the variability of the received signal strength from the transmitter as a result of changes in distance and orientation relative to the two receivers.

Animals were removed from their home-cages for the measurement of respiratory parameters, directly after the completion of the cardiovascular measurement at 1, 2 and 4 hours after dosing. Tracheal air flow was measured in conscious dogs using a sealed mask (covering the animals' snout) attached to a pneumotachograph and the pulmonary monitoring system PMX (Mumed Ltd., London).

3.10 TERMINATION OF THE EXPERIMENT

At the end of the study, all animals were retained at RCC.

3.11 DATA COMPILATION AND STATISTICAL ANALYSIS

Systolic, diastolic and mean arterial blood pressure, heart rate, ECG traces (Lead II), respiratory rate and tidal volume were recorded directly by a computer.

Respiratory rate was determined by using the number of zero flow signals. Tidal volume was calculated by integration of the inspiration flow signal recorded over each breathing cycle. Minute volume was calculated by multiplication of the two previous parameters. The mean values calculated over 10 minutes were entered manually into a VAX computer and/or EXCEL spreadsheet for compilation and statistical analysis.

ECG tracings were evaluated manually for P wave duration and amplitude, P-Q interval, QRS complex and Q-T interval using a representative section of electrocardiogram at the measurement time points. Values were entered manually into a VAX computer and/or EXCEL spreadsheet for compilation and statistical analysis.

For each parameter, percent change was calculated with reference to the respective values before each dosing (-30min).

Mean values and standard deviations from each parameter were calculated. Statistical analysis was carried out using the Dunnett many-to-one t-test. Values where $p<0.05$ were considered to be statistically significant from control (vehicle treated animals).

Clinical signs were recorded manually.

4 SUMMARY OF RESULTS

Hydroxymatairesinol was administered by gavage to four male dogs at doses of 2, 20 and 200 mg/kg, using a randomised design, with 4 –8 days between each dose. Systolic, diastolic and mean blood pressure, heart rate, electrocardiograms and locomotor activity were monitored before and for up to 12 hours after dosing. Clinical signs were noted at intervals for up to 24 hours after dosing. Respiratory rate, tidal volume were monitored and minute volume calculated, before and at approximately 1, 2 and 4 hours after dosing.

The results are presented in Figures 1 to 7 on pages 17 to 23 and in summary tables on pages 26 – 50. Individual values are shown in Attachment I (pages 53 – 95).

Following oral administration of Hydroxymatairesinol up to 200 mg/kg, no overt effects on systolic, diastolic and mean blood pressures and heart rate were evident. At 2 hours after treatment with 2mg/kg and 200 mg/kg, (but not 20 mg/kg), diastolic and mean blood pressures were lower than values recorded at 2 hours after treatment with empty capsules ($p<0.05$). Compared with the pre-dose values, the changes in diastolic blood pressure were small and were of the magnitude of –7.8 % (ns) and -11.6 % ($p<0.05$) and on mean blood pressure -9.4 % (ns) and –9.7 % (ns), respectively. In the absence of a similar effect following treatment with 20 mg/kg and no evidence of a dose-relationship, these findings are considered fortuitous and not related to treatment.

Following 2 mg/kg Hydroxymatairesinol, significantly higher values for heart rate were evident at 7 ($p<0.05$) and 12 hours ($p<0.05$) after dosing, resulting from the increased heart rates of two of the four animals (nos. 2 and 4) between 6 and 12 hours after dosing. The reasons for this finding are unclear as the locomotor activity of the two animals was relatively increased but not of comparable magnitude and as the two animals were not dosed with 2 mg/kg on the same day, environmental factors do not clearly play a role. When data were expressed as percent change from before dosing values, these effects were no longer statistically significant. No effect on heart rate was observed when animals were dosed with 20 or 200 mg/kg and therefore the effects seen at 2 mg/kg are not clearly related to treatment with the test item.

No effects on P-wave amplitude, P-wave duration, P-T, QRS or Q-T interval were measured following oral administration of vehicle, 2, 20 and 200 mg/kg Hydroxymatairesinol at intervals for up to 12 hours after dosing.

Administration of Hydroxymatairesinol, at doses up to 200 mg/kg had no overt effects on absolute values of respiratory rate, tidal volume and minute volume in the conscious dog, when measured at 1, 2 and 4 hours after dosing.

No clinical signs were observed following administration of vehicle and Hydroxymatairesinol at 2, 20 and 200 mg/kg for up to 24 hours after dosing.

5 CONCLUSION

Hydroxymatairesinol, at doses up to 200 mg/kg, was without overt effects on systolic, diastolic and mean blood pressure, heart rate and locomotor activity in the telemetered male dog. Electrocardiograms showed no changes in P-wave amplitude, P-wave duration, P-Q interval, QRS-interval or Q-T interval that could be related to administration of the test item.

At doses up to 200 mg/kg Hydroxymatairesinol was without effect on respiratory rate, tidal volume and minute volume in the conscious (telemetry) dog.

No clinical signs were observed following administration of vehicle and Hydroxymatairesinol at 2, 20 and 200 mg/kg for up to 24 hours after dosing.

6 FIGURES

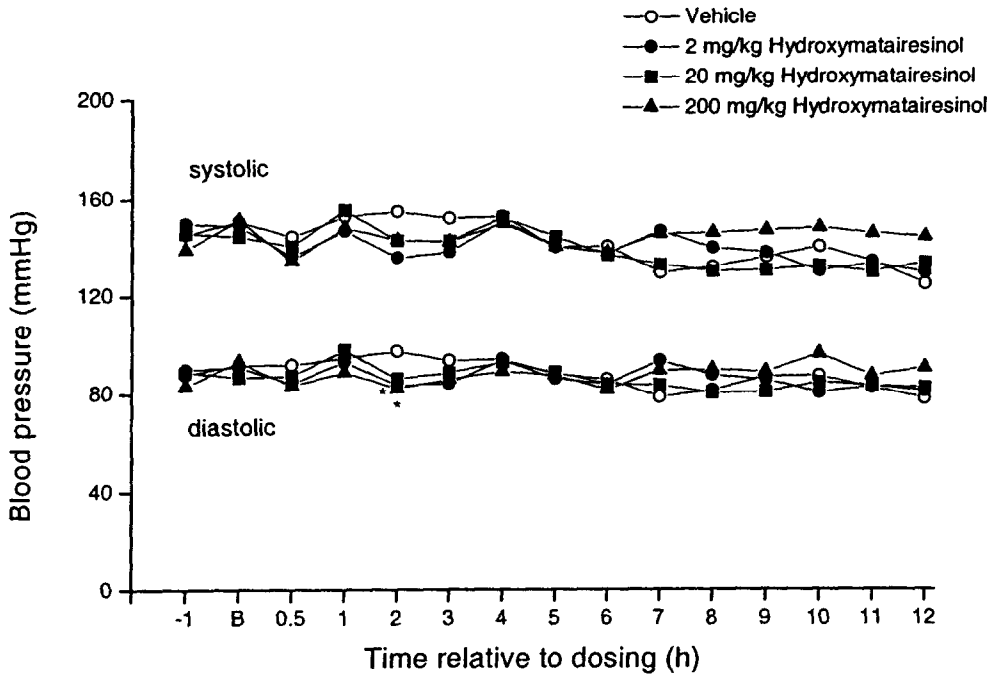

Figure 1: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on systolic and diastolic blood pressures (mmHg) following oral administration in the telemetered dog. B = before dosing; -1, 0.5, 1, 2.... = hours relative to dosing. Values are mean of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

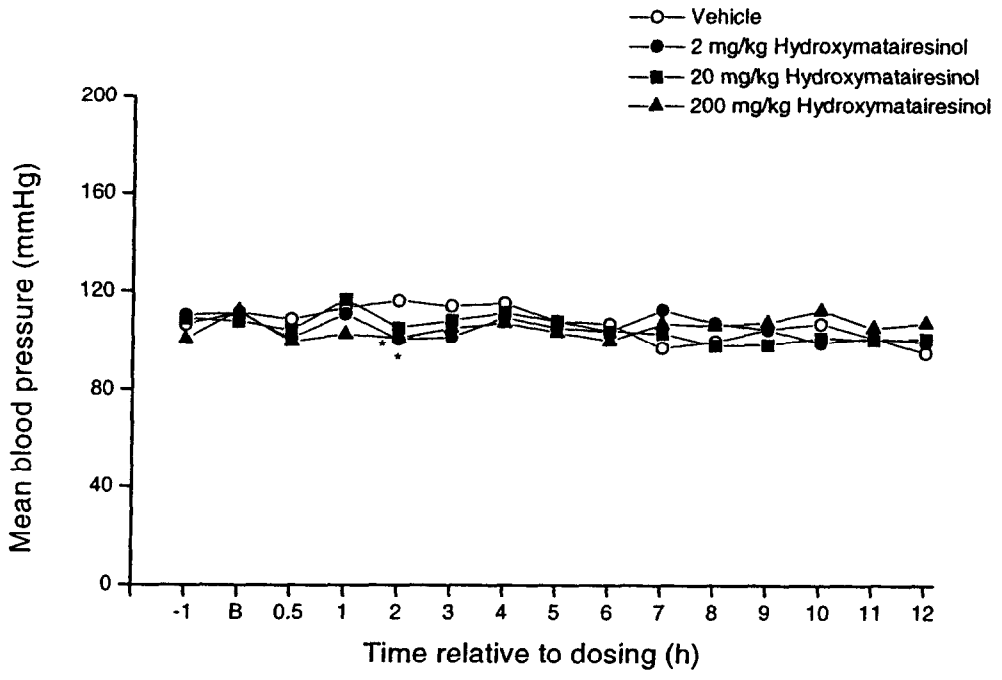

Figure 2: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on mean blood pressure (mmHg) following oral administration in the telemetered dog. B = before dosing; -1, 0.5, 1, 2.... = hours relative to dosing. Values are mean of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

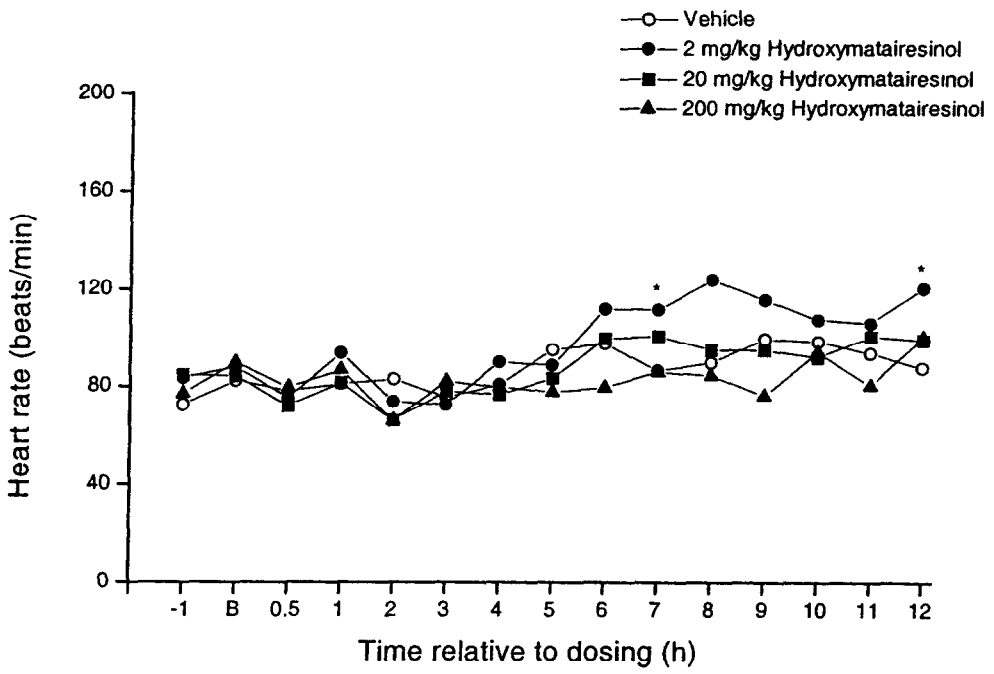

Figure 3: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on heart rate (beats / min) following oral administration in the telemetered dog. B = before dosing; -1, 0.5, 1, 2.... = hours relative to dosing. Values are mean of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

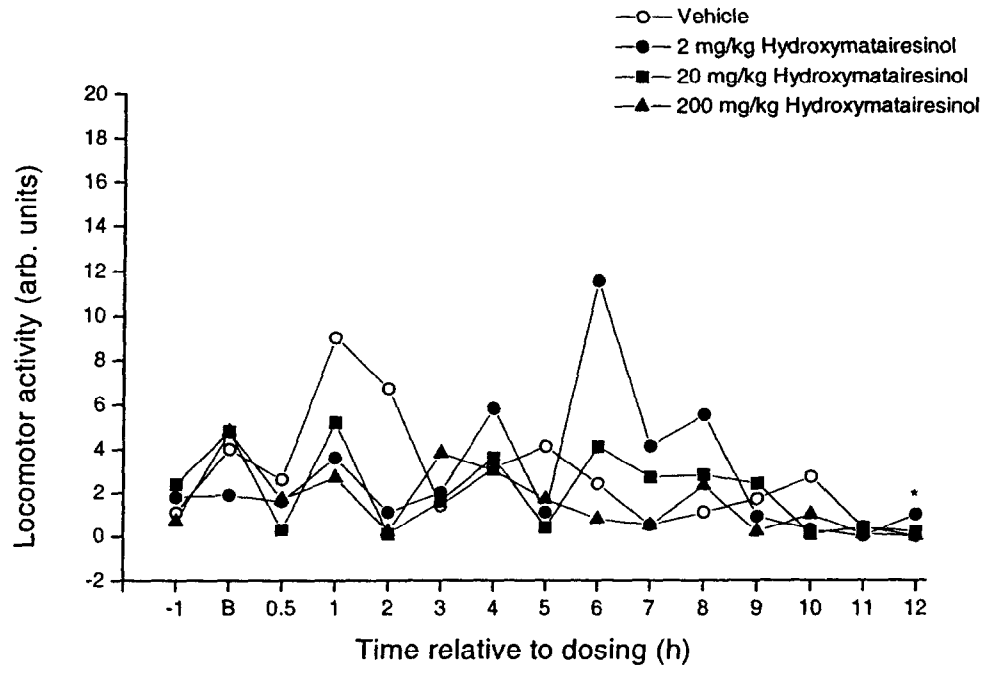

Figure 4: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on locomotor activity (arb. units) following oral administration in the telemetered dog. B = before dosing; -1, 0.5, 1, 2.... = hours relative to dosing. Values are mean of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

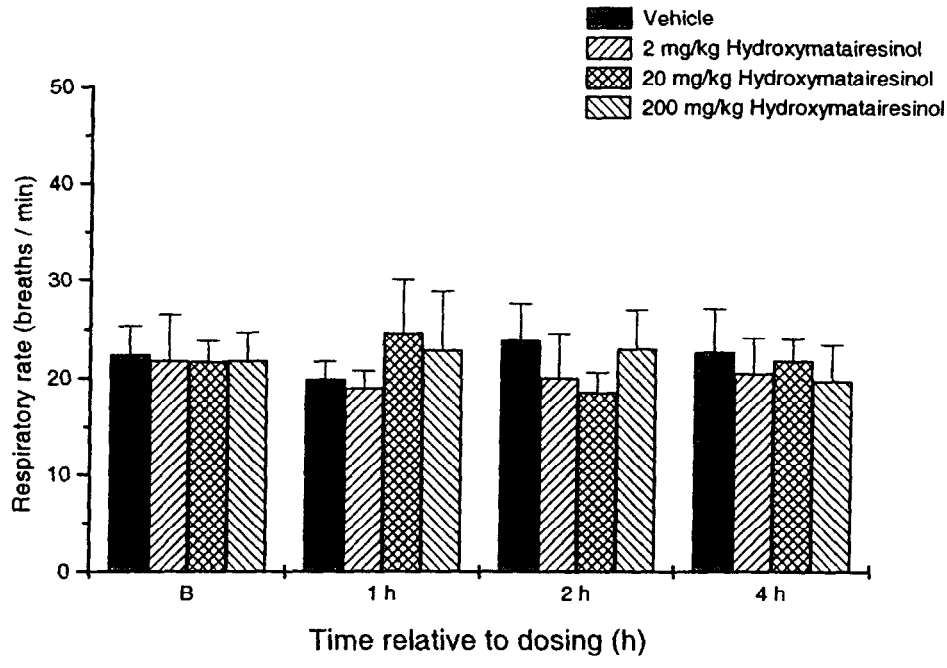

Figure 5: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on respiratory rate (breaths / min) following oral administration in the telemetered dog. B = before dosing; 1, 2 and 4 = hours relative to dosing. Values are mean + SD of 4 observations. *$p<0.05$, **$p<0.01$, Dunnett t-test.

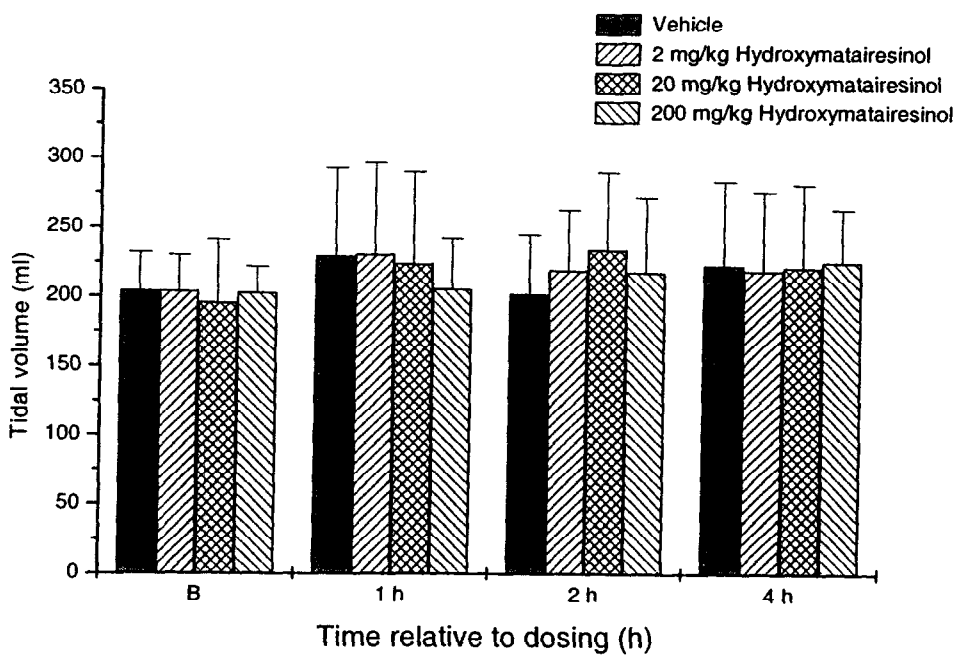

Figure 6: Effects of Hydroxymatairesinol (2, 20 and 200 mg/kg) or vehicle (empty capsule), on tidal volume (ml) following oral administration in the telemetered dog. B = before dosing 1, 2 and 4 = hours relative to dosing. Values are mean + SD of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

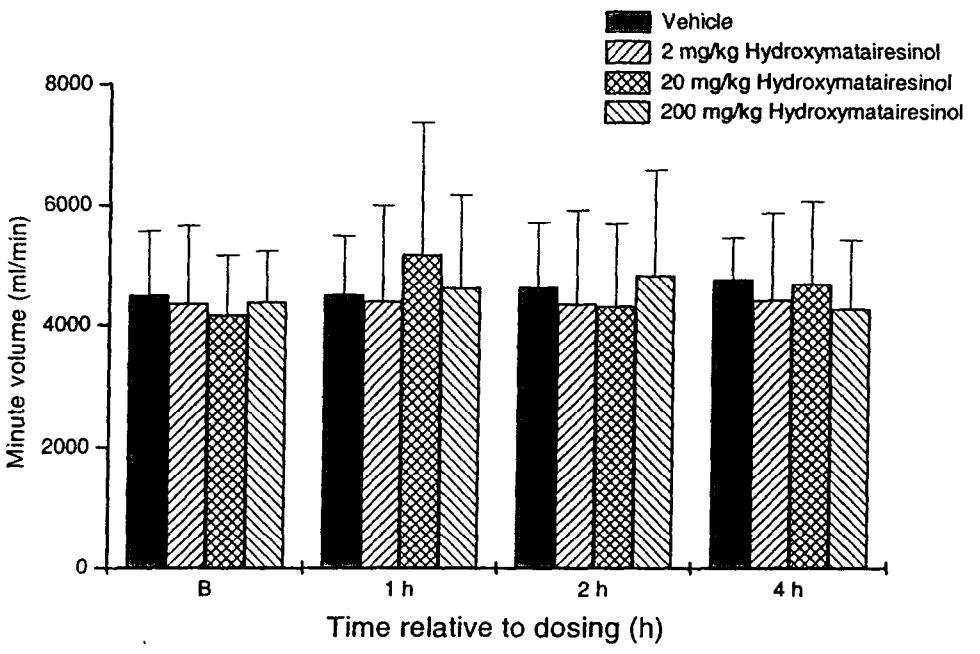

Figure 7: Effects of Hydroxymatairesinol (1, 10 and 100 mg/kg) or vehicle (empty capsule), on minute volume (ml/min) following oral administration in the telemetered dog. B = before dosing; 1, 2 and 4 = hours relative to dosing. Values are mean + SD of 4 observations. *p<0.05, **p<0.01, Dunnett t-test.

7 SUMMARY TABLES

SUMMARY TABLES (CONTINUED)

Before dosing = -30 minutes

RCC PROJECT 780625
HYDROXYMATAIRESINOL

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CARDIOVASCULAR PARAMETERS SUMMARY
Systolic Blood Pressure (mmHg)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	145.2	149.6	145.6	138.9
	ST.DEV.	15.5	9.1	23.7	9.2
	N	4	4	4	4
Before	MEAN	150.4	148.5	144.2	151.1
	ST.DEV.	19.7	11.0	21.1	15.3
	N	4	4	4	4
30 min	MEAN	144.1	135.9	140.2	134.1
	ST.DEV.	18.9	8.0	15.7	11.0
	N	4	4	4	4
1 hour	MEAN	152.4	146.4	154.9	147.7
	ST.DEV.	23.1	7.7	16.5	15.9
	N	4	4	4	4
2 hours	MEAN	154.2	135.3	142.4	142.6
	ST.DEV.	13.5	6.8	10.7	10.2
	N	4	4	4	4
3 hours	MEAN	151.5	137.5	142.2	141.8
	ST.DEV.	22.8	11.4	16.8	15.7
	N	4	4	4	4
4 hours	MEAN	152.2	150.4	151.8	149.4
	ST.DEV.	21.8	6.3	13.3	4.3
	N	4	4	4	4
5 hours	MEAN	139.6	139.7	143.9	139.8
	ST.DEV.	24.2	13.9	13.6	4.3
	N	4	4	4	4
6 hours	MEAN	139.8	137.0	136.3	137.4
	ST.DEV.	21.8	23.8	6.5	9.5
	N	4	4	4	4
7 hours	MEAN	129.2	146.2	132.5	145.1
	ST.DEV.	14.8	10.5	21.0	10.5
	N	4	4	4	4
8 hours	MEAN	131.4	139.3	129.7	145.5
	ST.DEV.	10.3	20.8	15.7	13.3
	N	4	4	4	4
9 hours	MEAN	135.5	137.4	130.1	146.5
	ST.DEV.	24.2	22.8	15.6	14.3
	N	4	4	4	4
10 hours	MEAN	139.9	129.8	132.0	147.6
	ST.DEV.	8.3	19.5	11.8	23.9
	N	4	4	4	4
11 hours	MEAN	133.8	132.8	129.4	145.2
	ST.DEV.	26.9	4.0	13.9	13.6
	N	4	4	4	4
12 hours	MEAN	124.5	129.0	133.1	143.8
	ST.DEV.	16.7	7.7	19.3	7.7
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

CARDIOVASCULAR PARAMETERS SUMMARY
Diastolic Blood Pressure (mmHg)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	87.7	89.7	88.7	82.9
	ST.DEV.	10.1	13.7	16.4	6.0
	N	4	4	4	4
Before	MEAN	91.6	90.6	86.5	92.9
	ST.DEV.	11.0	9.8	16.2	7.0
	N	4	4	4	4
30 min	MEAN	91.5	83.9	86.9	83.0
	ST.DEV.	7.9	6.7	15.1	2.9
	N	4	4	4	4
1 hour	MEAN	94.3	92.7	97.6	88.5
	ST.DEV.	14.8	5.3	11.7	12.3
	N	4	4	4	4
2 hours	MEAN	97.0	83.2 *	85.8	81.8 *
	ST.DEV.	4.5	8.7	10.0	3.0
	N	4	4	4	4
3 hours	MEAN	93.2	83.8	88.2	85.5
	ST.DEV.	13.4	12.3	11.0	7.4
	N	4	4	4	4
4 hours	MEAN	93.8	93.4	92.6	88.8
	ST.DEV.	15.6	6.1	13.5	4.4
	N	4	4	4	4
5 hours	MEAN	87.8	85.9	88.6	87.3
	ST.DEV.	14.2	5.5	10.9	4.7
	N	4	4	4	4
6 hours	MEAN	85.6	83.7	83.8	81.4
	ST.DEV.	19.5	12.8	9.1	4.0
	N	4	4	4	4
7 hours	MEAN	78.5	93.3	83.3	89.3
	ST.DEV.	10.8	5.8	19.8	10.4
	N	4	4	4	4
8 hours	MEAN	81.2	87.5	80.2	89.7
	ST.DEV.	10.6	10.8	9.2	2.8
	N	4	4	4	4
9 hours	MEAN	86.9	85.5	80.6	88.7
	ST.DEV.	18.8	11.4	18.5	5.0
	N	4	4	4	4
10 hours	MEAN	87.1	80.3	84.5	96.0
	ST.DEV.	7.8	12.0	10.7	13.0
	N	4	4	4	4
11 hours	MEAN	82.3	82.7	82.9	87.0
	ST.DEV.	19.2	8.9	6.1	3.7
	N	4	4	4	4
12 hours	MEAN	77.8	80.8	82.2	90.2
	ST.DEV.	14.7	13.8	9.0	5.3
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

CARDIOVASCULAR PARAMETERS SUMMARY
Mean Blood Pressure (mmHg)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	106.5	110.4	109.0	100.5
	ST.DEV.	11.1	12.6	17.2	7.3
	N	4	4	4	4
Before	MEAN	111.5	111.3	107.9	112.2
	ST.DEV.	13.3	9.3	17.1	12.1
	N	4	4	4	4
30 min	MEAN	108.8	101.0	104.4	99.6
	ST.DEV.	11.5	5.2	14.8	5.7
	N	4	4	4	4
1 hour	MEAN	113.3	110.8	116.7	102.6
	ST.DEV.	19.9	4.1	14.8	6.3
	N	4	4	4	4
2 hours	MEAN	116.1	100.4 *	105.1	100.8 *
	ST.DEV.	9.2	6.9	7.9	5.2
	N	4	4	4	4
3 hours	MEAN	113.9	101.1	108.0	104.9
	ST.DEV.	17.1	10.3	10.7	12.1
	N	4	4	4	4
4 hours	MEAN	115.0	109.2	111.2	107.0
	ST.DEV.	18.7	5.9	10.1	3.5
	N	4	4	4	4
5 hours	MEAN	107.7	104.9	107.6	103.1
	ST.DEV.	19.2	8.5	9.3	2.4
	N	4	4	4	4
6 hours	MEAN	106.5	103.4	103.6	99.6
	ST.DEV.	18.9	18.4	5.3	4.6
	N	4	4	4	4
7 hours	MEAN	96.6	112.2	102.6	106.5
	ST.DEV.	10.5	8.1	19.2	10.8
	N	4	4	4	4
8 hours	MEAN	99.5	106.9	97.9	105.9
	ST.DEV.	7.3	13.8	9.4	7.0
	N	4	4	4	4
9 hours	MEAN	104.4	104.3	98.1	107.2
	ST.DEV.	19.9	16.3	15.9	8.0
	N	4	4	4	4
10 hours	MEAN	106.7	98.8	101.0	112.1
	ST.DEV.	3.3	13.5	8.3	18.0
	N	4	4	4	4
11 hours	MEAN	101.0	101.1	100.1	105.0
	ST.DEV.	18.9	4.9	6.5	5.4
	N	4	4	4	4
12 hours	MEAN	94.8	99.1	100.7	107.1
	ST.DEV.	13.3	10.2	10.5	5.0
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

CARDIOVASCULAR PARAMETERS SUMMARY
Heart Rate (bpm)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	72.3	83.4	84.7	76.9
	ST.DEV.	11.8	16.1	8.6	12.1
	N	4	4	4	4
Before	MEAN	82.4	88.2	84.3	89.9
	ST.DEV.	6.5	8.9	14.1	4.2
	N	4	4	4	4
30 min	MEAN	78.2	75.2	72.0	79.6
	ST.DEV.	13.2	8.0	2.7	7.7
	N	4	4	4	4
1 hour	MEAN	81.1	93.8	81.5	86.8
	ST.DEV.	26.3	21.3	11.8	8.7
	N	4	4	4	4
2 hours	MEAN	82.9	73.6	66.0	66.0
	ST.DEV.	21.9	6.4	5.6	6.9
	N	4	4	4	4
3 hours	MEAN	75.4	72.3	77.9	82.1
	ST.DEV.	12.5	10.0	21.3	13.1
	N	4	4	4	4
4 hours	MEAN	80.7	90.1	76.6	79.7
	ST.DEV.	10.8	4.9	9.2	18.3
	N	4	4	4	4
5 hours	MEAN	95.2	88.7	83.3	77.7
	ST.DEV.	12.4	9.4	11.4	14.0
	N	4	4	4	4
6 hours	MEAN	97.8	111.9	99.8	79.6
	ST.DEV.	12.7	11.7	12.8	21.6
	N	4	4	4	4
7 hours	MEAN	86.6	117.7 *	100.7	86.0
	ST.DEV.	6.4	21.1	5.8	11.1
	N	4	4	4	4
8 hours	MEAN	89.8	123.9	95.1	84.5
	ST.DEV.	14.4	30.8	14.9	22.7
	N	4	4	4	4
9 hours	MEAN	99.5	115.6	95.0	76.0
	ST.DEV.	11.5	18.3	23.4	17.6
	N	4	4	4	4
10 hours	MEAN	98.4	107.4	91.9	94.0
	ST.DEV.	18.4	10.6	11.4	12.4
	N	4	4	4	4
11 hours	MEAN	93.7	106.0	100.5	80.3
	ST.DEV.	10.4	10.4	19.3	21.2
	N	4	4	4	4
12 hours	MEAN	87.7	120.5 *	99.1	100.1
	ST.DEV.	9.6	16.1	14.4	12.6
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

ELECTROCARDIOGRAMS SUMMARY
P-Wave Amplitude (mV)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	0.17	0.14	0.15	0.14
	ST.DEV.	0.08	0.07	0.09	0.06
	N	4	4	4	4
Before	MEAN	0.16	0.15	0.14	0.13
	ST.DEV.	0.08	0.05	0.05	0.06
	N	4	4	4	4
30 min	MEAN	0.15	0.20	0.14	0.15
	ST.DEV.	0.09	0.10	0.09	0.06
	N	4	4	4	4
1 hour	MEAN	0.16	0.18	0.14	0.17
	ST.DEV.	0.09	0.06	0.06	0.10
	N	4	4	4	4
2 hours	MEAN	0.13	0.19	0.13	0.16
	ST.DEV.	0.07	0.06	0.07	0.08
	N	4	4	4	4
3 hours	MEAN	0.12	0.18	0.12	0.13
	ST.DEV.	0.04	0.07	0.06	0.04
	N	4	4	4	4
4 hours	MEAN	0.14	0.14	0.15	0.13
	ST.DEV.	0.09	0.05	0.05	0.05
	N	4	4	4	4
12 hours	MEAN	0.17	0.18	0.24	0.19
	ST.DEV.	0.14	0.08	0.16	0.09
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

ELECTROCARDIOGRAMS SUMMARY
P-Wave Duration (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	39.00	39.75	38.75	39.50
	ST.DEV.	3.83	2.63	0.96	2.38
	N	4	4	4	4
Before	MEAN	39.75	39.00	42.00	39.50
	ST.DEV.	1.50	4.16	2.45	1.29
	N	4	4	4	4
30 min	MEAN	38.00	39.25	38.75	38.50
	ST.DEV.	2.45	2.99	3.40	2.65
	N	4	4	4	4
1 hour	MEAN	40.50	41.50	37.00	39.25
	ST.DEV.	3.79	3.32	3.74	2.99
	N	4	4	4	4
2 hours	MEAN	36.25	39.75	41.25	38.00
	ST.DEV.	4.11	4.79	0.96	4.08
	N	4	4	4	4
3 hours	MEAN	39.25	41.25	36.00	38.00
	ST.DEV.	4.99	2.99	2.16	3.37
	N	4	4	4	4
4 hours	MEAN	41.00	39.75	39.00	39.00
	ST.DEV.	1.15	2.36	3.37	3.56
	N	4	4	4	4
12 hours	MEAN	38.00	39.25	38.25	38.50
	ST.DEV.	4.55	1.89	2.87	4.51
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

ELECTROCARDIOGRAMS SUMMARY
P-Q Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	92.50	95.75	91.00	93.25
	ST.DEV.	6.56	2.75	6.16	5.12
	N	4	4	4	4
Before	MEAN	89.50	91.75	94.50	92.50
	ST.DEV.	3.32	6.65	5.80	9.68
	N	4	4	4	4
30 min	MEAN	94.50	97.25	98.50	98.00
	ST.DEV.	4.43	7.37	6.19	5.72
	N	4	4	4	4
1 hour	MEAN	95.25	98.25	90.75	95.25
	ST.DEV.	5.32	6.85	5.25	6.40
	N	4	4	4	4
2 hours	MEAN	94.25	99.75	96.25	94.75
	ST.DEV.	4.86	8.69	3.59	4.99
	N	4	4	4	4
3 hours	MEAN	91.75	97.25	96.75	97.75
	ST.DEV.	1.71	7.85	6.24	7.68
	N	4	4	4	4
4 hours	MEAN	93.50	94.00	93.00	95.00
	ST.DEV.	3.00	3.27	7.39	6.06
	N	4	4	4	4
12 hours	MEAN	89.00	82.50	89.75	89.25
	ST.DEV.	10.98	2.89	4.50	15.13
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

ELECTROCARDIOGRAMS SUMMARY
QRS Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	47.50	50.75	47.50	46.50
	ST.DEV.	7.19	4.99	3.00	5.92
	N	4	4	4	4
Before	MEAN	45.50	51.00	49.75	50.00
	ST.DEV.	3.70	5.35	4.79	2.16
	N	4	4	4	4
30 min	MEAN	44.50	50.25	48.50	48.50
	ST.DEV.	3.11	4.43	4.43	4.43
	N	4	4	4	4
1 hour	MEAN	47.75	52.00	49.00	48.00
	ST.DEV.	3.86	4.08	2.00	6.27
	N	4	4	4	4
2 hours	MEAN	45.75	51.50	48.50	47.50
	ST.DEV.	7.14	3.79	4.36	5.20
	N	4	4	4	4
3 hours	MEAN	49.00	49.75	49.50	48.25
	ST.DEV.	5.03	4.57	5.26	5.68
	N	4	4	4	4
4 hours	MEAN	49.50	49.25	49.50	48.75
	ST.DEV.	4.93	4.99	4.12	3.86
	N	4	4	4	4
12 hours	MEAN	51.75	49.75	48.25	50.50
	ST.DEV.	1.26	2.06	3.59	5.45
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

ELECTROCARDIOGRAMS SUMMARY
Q-T Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	227.00	227.50	224.25	222.25
	ST.DEV.	14.58	11.62	10.08	7.76
	N	4	4	4	4
Before	MEAN	223.00	221.75	229.25	222.25
	ST.DEV.	8.52	9.50	18.75	5.91
	N	4	4	4	4
30 min	MEAN	217.25	225.50	229.75	226.00
	ST.DEV.	16.88	14.25	16.62	12.27
	N	4	4	4	4
1 hour	MEAN	217.00	215.75	224.00	227.50
	ST.DEV.	11.40	8.18	10.80	17.31
	N	4	4	4	4
2 hours	MEAN	212.75	226.25	235.00	226.75
	ST.DEV.	14.73	9.54	10.68	16.68
	N	4	4	4	4
3 hours	MEAN	224.00	226.75	226.75	225.75
	ST.DEV.	4.32	8.42	16.36	12.47
	N	4	4	4	4
4 hours	MEAN	221.00	223.50	226.50	227.75
	ST.DEV.	5.77	15.26	17.10	8.42
	N	4	4	4	4
12 hours	MEAN	225.25	210.50	213.75	222.75
	ST.DEV.	7.14	8.06	9.03	16.26
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RESPIRATORY PARAMETERS SUMMARY
Respiratory Rate (brpm)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
Before	MEAN	22.4	21.8	21.7	21.8
	ST.DEV.	2.9	4.7	2.1	2.9
	N	4	4	4	4
1 hour	MEAN	19.9	19.0	24.6	22.8
	ST.DEV.	1.8	1.7	5.4	6.0
	N	4	4	4	4
2 hours	MEAN	23.8	20.0	18.5	22.9
	ST.DEV.	3.7	4.5	2.0	4.0
	N	4	4	4	4
4 hours	MEAN	22.6	20.4	21.7	19.7
	ST.DEV.	4.4	3.6	2.2	3.6
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

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HYDROXYMATAIRESINOL

RESPIRATORY PARAMETERS SUMMARY
Tidal Volume (ml)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
Before	MEAN	204.04	203.83	195.44	202.70
	ST.DEV.	27.84	25.89	45.28	18.83
	N	4	4	4	4
1 hour	MEAN	229.07	230.15	223.47	205.15
	ST.DEV.	63.30	65.75	65.91	36.04
	N	4	4	4	4
2 hours	MEAN	201.33	218.70	233.54	217.31
	ST.DEV.	42.63	43.81	55.40	53.86
	N	4	4	4	4
4 hours	MEAN	222.25	218.21	220.75	224.59
	ST.DEV.	60.17	56.95	59.34	38.28
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

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RESPIRATORY PARAMETERS SUMMARY
Minute Volume (ml/min)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
Before	MEAN	4486.7	4350.1	4164.1	4371.6
	ST.DEV.	1069.7	1296.8	994.0	853.8
	N	4	4	4	4
1 hour	MEAN	4493.5	4390.3	5166.1	4609.7
	ST.DEV.	979.2	1598.6	2184.3	1548.0
	N	4	4	4	4
2 hours	MEAN	4623.0	4344.9	4308.7	4823.0
	ST.DEV.	1068.0	1556.4	1367.6	1731.2
	N	4	4	4	4
4 hours	MEAN	4755.6	4414.4	4691.0	4274.4
	ST.DEV.	688.6	1445.6	1359.7	1133.6
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RCC PROJECT 780625
HYDROXYMATAIRESINOL

LOCOMOTOR ACTIVITY SUMMARY
ARB. UNITS
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
-60 min	MEAN	1.1	1.8	2.4	0.7
	ST.DEV.	2.1	2.4	3.2	0.8
	N	4	4	4	4
Before	MEAN	4.0	1.9	4.8	4.8
	ST.DEV.	3.9	1.5	3.5	2.9
	N	4	4	4	4
30 min	MEAN	2.6	1.6	0.3	1.7
	ST.DEV.	3.3	1.1	0.5	0.7
	N	4	4	4	4
1 hour	MEAN	9.0	3.6	5.2	2.7
	ST.DEV.	14.6	2.4	6.8	2.9
	N	4	4	4	4
2 hours	MEAN	6.7	1.1	0.1	0.2
	ST.DEV.	6.9	2.2	0.1	0.3
	N	4	4	4	4
3 hours	MEAN	1.4	2.0	1.6	3.8
	ST.DEV.	1.8	3.9	1.8	4.1
	N	4	4	4	4
4 hours	MEAN	3.1	5.8	3.6	3.0
	ST.DEV.	2.5	2.6	4.2	2.8
	N	4	4	4	4
5 hours	MEAN	4.1	1.1	0.4	1.7
	ST.DEV.	5.7	1.3	0.7	2.5
	N	4	4	4	4
6 hours	MEAN	2.4	11.5	4.1	0.8
	ST.DEV.	3.2	14.6	4.4	1.0
	N	4	4	4	4
7 hours	MEAN	0.5	4.1	2.7	0.5
	ST.DEV.	0.9	4.6	2.4	0.9
	N	4	4	4	4
8 hours	MEAN	1.1	5.5	2.8	2.3
	ST.DEV.	2.1	6.4	5.5	4.2
	N	4	4	4	4
9 hours	MEAN	1.7	0.9	2.4	0.2
	ST.DEV.	1.4	0.8	4.6	0.2
	N	4	4	4	4
10 hours	MEAN	2.7	0.3	0.1	1.0
	ST.DEV.	5.4	0.5	0.2	1.2
	N	4	4	4	4
11 hours	MEAN	0.4	0.0	0.4	0.1
	ST.DEV.	0.8	0.0	0.8	0.1
	N	4	4	4	4
12 hours	MEAN	0.0	1.0 *	0.2	0.0
	ST.DEV.	0.0	0.9	0.3	0.0
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

CARDIOVASCULAR PARAMETERS (% CHANGE) SUMMARY
Systolic Blood Pressure
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-4.1	-8.1	-1.9	-10.9
	ST.DEV.	4.9	9.0	12.4	6.6
	N	4	4	4	4
1 hour	MEAN	1.4	-1.2	8.4	-2.2
	ST.DEV.	9.4	4.3	13.3	4.1
	N	4	4	4	4
2 hours	MEAN	3.1	-8.5	-0.4	-5.4
	ST.DEV.	8.7	8.0	8.6	4.3
	N	4	4	4	4
3 hours	MEAN	0.6	-7.1	-0.9	-6.2
	ST.DEV.	5.9	8.6	9.1	3.5
	N	4	4	4	4
4 hours	MEAN	1.3	1.6	6.0	-0.6
	ST.DEV.	9.6	5.9	7.9	7.4
	N	4	4	4	4
5 hours	MEAN	-7.5	-5.7	0.4	-6.8
	ST.DEV.	6.0	8.8	6.0	9.3
	N	4	4	4	4
6 hours	MEAN	-7.2	-7.7	-4.5	-8.7
	ST.DEV.	4.2	14.3	9.1	6.6
	N	4	4	4	4
7 hours	MEAN	-13.9	-1.2	-8.1	-3.5
	ST.DEV.	5.1	7.9	5.9	7.6
	N	4	4	4	4
8 hours	MEAN	-11.8	-6.2	-9.8	-3.2
	ST.DEV.	10.2	11.9	4.8	10.9
	N	4	4	4	4
9 hours	MEAN	-10.2	-7.6	-9.3	-2.5
	ST.DEV.	6.4	12.7	7.6	11.5
	N	4	4	4	4
10 hours	MEAN	-6.4	-12.6	-7.8	-2.5
	ST.DEV.	6.3	11.2	6.3	10.1
	N	4	4	4	4
11 hours	MEAN	-11.5	-10.2	-9.8	-3.5
	ST.DEV.	8.0	5.7	5.6	9.7
	N	4	4	4	4
12 hours	MEAN	-17.0	-12.8	-7.4	-4.4
	ST.DEV.	7.5	7.5	8.9	6.8
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

CARDIOVASCULAR PARAMETERS (% CHANGE) SUMMARY
Diastolic Blood Pressure
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	0.3	-6.8	1.4	-10.4
	ST.DEV.	6.5	8.7	15.1	5.1
	N	4	4	4	4
1 hour	MEAN	3.2	2.9	14.7	-5.0
	ST.DEV.	14.1	6.7	19.1	8.2
	N	4	4	4	4
2 hours	MEAN	7.0	-7.8	0.3	-11.6 *
	ST.DEV.	13.0	8.3	8.6	5.2
	N	4	4	4	4
3 hours	MEAN	1.6	-7.2	3.2	-8.0
	ST.DEV.	6.8	11.6	12.6	1.9
	N	4	4	4	4
4 hours	MEAN	2.6	3.6	7.9	-4.1
	ST.DEV.	15.8	8.2	9.5	8.0
	N	4	4	4	4
5 hours	MEAN	-4.4	-4.7	3.4	-5.6
	ST.DEV.	7.7	7.4	7.0	9.0
	N	4	4	4	4
6 hours	MEAN	-7.5	-7.1	-1.4	-12.2
	ST.DEV.	10.7	14.9	14.5	4.2
	N	4	4	4	4
7 hours	MEAN	-14.4	3.5 *	-4.2	-3.8
	ST.DEV.	4.4	7.8	7.2	9.9
	N	4	4	4	4
8 hours	MEAN	-11.1	-3.3	-6.1	-2.9
	ST.DEV.	9.6	7.4	9.9	9.5
	N	4	4	4	4
9 hours	MEAN	-5.9	-5.2	-6.3	-4.1
	ST.DEV.	9.8	12.2	14.1	9.4
	N	4	4	4	4
10 hours	MEAN	-4.4	-11.4	-0.9	3.1
	ST.DEV.	8.6	8.7	12.5	8.0
	N	4	4	4	4
11 hours	MEAN	-11.0	-8.4	-2.4	-6.1
	ST.DEV.	10.5	7.7	14.0	6.5
	N	4	4	4	4
12 hours	MEAN	-15.5	-10.6	-3.8	-2.7
	ST.DEV.	7.5	12.8	10.8	5.3
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

CARDIOVASCULAR PARAMETERS (% CHANGE) SUMMARY
Mean Blood Pressure
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-2.2	-8.9	-2.3	-10.7
	ST.DEV.	5.6	7.2	14.7	7.6
	N	4	4	4	4
1 hour	MEAN	1.6	-0.1	9.3	-8.2
	ST.DEV.	13.5	4.9	17.1	5.7
	N	4	4	4	4
2 hours	MEAN	4.9	-9.4	-1.6	-9.7
	ST.DEV.	11.6	7.8	9.6	5.8
	N	4	4	4	4
3 hours	MEAN	2.0	-8.8	1.1	-6.5
	ST.DEV.	7.2	10.5	12.1	4.9
	N	4	4	4	4
4 hours	MEAN	3.3	-1.5	4.1	-3.8
	ST.DEV.	13.9	7.4	11.0	10.9
	N	4	4	4	4
5 hours	MEAN	-3.8	-5.5	0.6	-7.2
	ST.DEV.	8.1	7.1	7.2	11.2
	N	4	4	4	4
6 hours	MEAN	-4.9	-7.0	-2.5	-10.7
	ST.DEV.	7.2	15.7	13.3	7.2
	N	4	4	4	4
7 hours	MEAN	-13.2	1.2 *	-5.1	-4.9
	ST.DEV.	5.3	8.9	7.4	6.8
	N	4	4	4	4
8 hours	MEAN	-10.0	-4.0	-8.5	-4.6
	ST.DEV.	9.9	9.6	8.9	14.0
	N	4	4	4	4
9 hours	MEAN	-6.9	-6.2	-8.3	-3.7
	ST.DEV.	7.2	12.8	12.5	10.6
	N	4	4	4	4
10 hours	MEAN	-3.5	-11.3	-5.3	-0.4
	ST.DEV.	8.4	9.6	10.2	6.4
	N	4	4	4	4
11 hours	MEAN	-9.9	-8.9	-6.1	-5.9
	ST.DEV.	7.3	4.9	10.9	7.5
	N	4	4	4	4
12 hours	MEAN	-14.9	-10.7	-5.9	-4.0
	ST.DEV.	7.0	9.7	8.9	7.2
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

CARDIOVASCULAR PARAMETERS (% CHANGE) SUMMARY
Heart Rate
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-4.9	-14.3	-12.9	-11.1
	ST.DEV.	15.1	9.8	13.7	11.7
	N	4	4	4	4
1 hour	MEAN	0.1	6.0	-1.7	-3.4
	ST.DEV.	37.3	17.4	17.4	7.6
	N	4	4	4	4
2 hours	MEAN	0.6	-16.2	-19.1	-26.4
	ST.DEV.	25.1	7.5	20.8	8.0
	N	4	4	4	4
3 hours	MEAN	-8.6	-17.9	-6.0	-8.6
	ST.DEV.	12.7	9.3	25.9	13.8
	N	4	4	4	4
4 hours	MEAN	-1.7	2.9	-8.5	-11.5
	ST.DEV.	14.2	10.4	6.2	18.6
	N	4	4	4	4
5 hours	MEAN	16.3	1.6	1.4	-13.8
	ST.DEV.	19.2	17.1	23.6	13.0
	N	4	4	4	4
6 hours	MEAN	19.1	28.9	22.2	-11.7
	ST.DEV.	16.4	26.0	32.8	22.2
	N	4	4	4	4
7 hours	MEAN	5.8	35.8	23.0	-4.4
	ST.DEV.	12.7	36.5	28.9	10.2
	N	4	4	4	4
8 hours	MEAN	9.6	43.3	17.5	-6.6
	ST.DEV.	18.6	46.7	39.3	21.7
	N	4	4	4	4
9 hours	MEAN	21.4	32.3	14.6	-15.8
	ST.DEV.	17.5	26.6	28.8	17.4
	N	4	4	4	4
10 hours	MEAN	20.0	22.8	11.7	4.3
	ST.DEV.	23.5	18.6	24.1	9.4
	N	4	4	4	4
11 hours	MEAN	13.6	21.8	23.9	-11.2
	ST.DEV.	4.8	22.6	40.9	20.4
	N	4	4	4	4
12 hours	MEAN	6.6	37.9	21.3	11.2
	ST.DEV.	10.5	23.7	33.1	9.9
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ELECTROCARDIOGRAMS (% CHANGE) SUMMARY
P-Wave Amplitude (mV)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-13.3	32.3	-4.8	21.1
	ST.DEV.	13.6	40.6	31.8	12.3
	N	4	4	4	4
1 hour	MEAN	-3.6	25.6	5.5	29.2
	ST.DEV.	14.6	50.1	27.9	20.2
	N	4	4	4	4
2 hours	MEAN	-21.5	35.4 **	-5.8	31.3 **
	ST.DEV.	16.5	18.1	25.5	18.4
	N	4	4	4	4
3 hours	MEAN	-25.9	33.9	-14.5	12.4
	ST.DEV.	18.4	79.4	25.9	30.1
	N	4	4	4	4
4 hours	MEAN	-17.8	-3.6	9.8	10.3
	ST.DEV.	14.7	28.8	17.6	16.3
	N	4	4	4	4
12 hours	MEAN	-3.4	17.7	70.4	52.0
	ST.DEV.	33.0	31.3	92.8	33.1
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

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ELECTROCARDIOGRAMS (% CHANGE) SUMMARY
P-Wave Duration (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-4.4	1.1	-7.7	-2.6
	ST.DEV.	3.8	7.5	6.5	5.0
	N	4	4	4	4
1 hour	MEAN	2.0	6.8	-12.1	-0.6
	ST.DEV.	11.0	7.1	3.9	6.8
	N	4	4	4	4
2 hours	MEAN	-8.9	1.8	-1.5	-3.9
	ST.DEV.	8.0	4.0	6.4	7.7
	N	4	4	4	4
3 hours	MEAN	-1.2	6.2	-14.2	-3.9
	ST.DEV.	12.0	7.2	4.9	6.3
	N	4	4	4	4
4 hours	MEAN	3.2	2.4	-7.0	-1.4
	ST.DEV.	4.4	6.4	8.9	6.7
	N	4	4	4	4
12 hours	MEAN	-4.5	1.8	-9.0	-2.7
	ST.DEV.	10.0	15.2	1.6	8.4
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ELECTROCARDIOGRAMS (% CHANGE) SUMMARY
P-Q Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	5.6	6.1	4.3	6.5
	ST.DEV.	2.7	5.4	4.9	7.6
	N	4	4	4	4
1 hour	MEAN	6.5	7.2	-3.9 *	3.4
	ST.DEV.	6.1	4.9	3.4	6.5
	N	4	4	4	4
2 hours	MEAN	5.3	8.7	2.0	3.2
	ST.DEV.	2.4	5.3	4.2	10.3
	N	4	4	4	4
3 hours	MEAN	2.6	6.1	2.5	6.6
	ST.DEV.	3.5	6.6	5.2	13.6
	N	4	4	4	4
4 hours	MEAN	4.6	2.7	-1.6	3.1
	ST.DEV.	4.6	5.6	5.3	5.3
	N	4	4	4	4
12 hours	MEAN	-0.4	-9.7	-4.6	-2.8
	ST.DEV.	13.2	7.5	10.0	18.3
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ELECTROCARDIOGRAMS (% CHANGE) SUMMARY
QRS Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-2.1	-1.0	-2.5	-3.0
	ST.DEV.	3.7	8.5	1.8	7.1
	N	4	4	4	4
1 hour	MEAN	5.1	2.2	-1.1	-4.1
	ST.DEV.	6.0	3.6	6.2	10.6
	N	4	4	4	4
2 hours	MEAN	1.2	1.3	-2.3	-5.1
	ST.DEV.	18.4	3.9	6.2	7.7
	N	4	4	4	4
3 hours	MEAN	7.7	-2.3	-0.5	-3.6
	ST.DEV.	8.0	1.8	5.3	8.8
	N	4	4	4	4
4 hours	MEAN	8.9	-3.4 *	-0.4	-2.4
	ST.DEV.	8.4	3.1	2.6	7.7
	N	4	4	4	4
12 hours	MEAN	14.4	-1.5	-2.9	0.8
	ST.DEV.	11.0	12.5	2.4	7.2
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ELECTROCARDIOGRAMS (% CHANGE) SUMMARY
Q-T Interval (ms)
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
30 min	MEAN	-2.6	1.8	0.4	1.7
	ST.DEV.	5.9	6.9	5.3	4.4
	N	4	4	4	4
1 hour	MEAN	-2.6	-2.7	-1.9	2.3
	ST.DEV.	4.8	2.0	7.6	5.9
	N	4	4	4	4
2 hours	MEAN	-4.7	2.1	2.8	2.0
	ST.DEV.	3.2	2.2	5.0	7.2
	N	4	4	4	4
3 hours	MEAN	0.5	2.3	-1.0	1.6
	ST.DEV.	3.3	1.6	2.3	6.2
	N	4	4	4	4
4 hours	MEAN	-0.7	0.8	-0.9	2.5
	ST.DEV.	5.9	5.9	8.0	3.9
	N	4	4	4	4
12 hours	MEAN	1.2	-5.0	-6.5	0.3
	ST.DEV.	7.2	4.9	4.1	8.4
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RESPIRATORY PARAMETERS (% CHANGE) SUMMARY
Respiratory Rate
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
1 hour	MEAN	-9.8	-10.9	12.4	5.2
	ST.DEV.	15.5	12.8	16.1	28.9
	N	4	4	4	4
2 hours	MEAN	6.8	-8.0	-14.6	5.5
	ST.DEV.	18.1	7.8	7.5	15.7
	N	4	4	4	4
4 hours	MEAN	3.1	-4.5	-0.1	-7.7
	ST.DEV.	29.4	16.4	4.8	23.3
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

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RESPIRATORY PARAMETERS (% CHANGE) SUMMARY
Tidal Volume
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
1 hour	MEAN	11.3	11.7	14.1	0.9
	ST.DEV.	21.2	22.6	17.7	10.4
	N	4	4	4	4
2 hours	MEAN	-1.9	6.6	19.7	6.1
	ST.DEV.	11.5	8.5	7.8	17.1
	N	4	4	4	4
4 hours	MEAN	7.7	6.0	13.3	10.4
	ST.DEV.	18.0	18.7	17.3	11.2
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

RESPIRATORY PARAMETERS (% CHANGE) SUMMARY
Minute Volume
MALES

		VEHICLE	2 MG/KG	20 MG/KG	200 MG/KG
TIME RELATIVE TO DOSING					
1 hour	MEAN	0.7	-0.2	22.1	4.1
	ST.DEV.	9.1	15.0	33.1	21.9
	N	4	4	4	4
2 hours	MEAN	3.6	-1.4	1.9	8.8
	ST.DEV.	9.8	10.5	9.3	22.1
	N	4	4	4	4
4 hours	MEAN	8.1	0.9	12.4	-1.9
	ST.DEV.	13.4	4.1	14.6	17.5
	N	4	4	4	4

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.